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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,690	10/06/2000	David B. Weiner	UPN-3906	1044

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EXAMINER	
LI, QIAN J	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/680,690	WEINER ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *14-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Reply to Restriction Requirement filed on Feb. 7, 2002 has been entered and assigned as Paper #7.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6, and 8-13, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that claim 1 is a generic claim directed at methods of delivering compounds to cells that express costimulatory molecules and is not limited to the two subgenuses, i.e. nucleic acids and proteins, that an election of species may have been appropriate. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are independent methods for delivering different molecules that belong to distinct chemical entities. The different molecules possess distinct chemical structure, physical property, and modes of operation in cell entry and in intracellular functioning, thus, the method of delivering such is deemed distinct. It is acknowledged that the compound recited in claim 1 is not limited to nucleic acids and proteins, and that claims drawn to different molecules other than nucleic acids and proteins may be examined in a divisional application, however, they are distinct inventions rather than different species. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is

not co-extensive, as indicated by separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-31 are pending, however, claims 7, and 14-31 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-6, and 8-13 are under current examination.

Priority

This application claims priority to US provisional application 60/157,871, filed October 6, 1999.

Claim Objections

Claims 2, 11, and 13 are objected to because these claims contain subject matter drawn to a non-elected invention (protein, protein complex, or therapeutic protein). The claims should be amended so that they only read on the elected invention. Appropriate correction is required.

Claim R jections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to methods of introducing a compound into a cell that express costimulatory molecules. The specification defines the term compound "is meant to refer to any molecule including but not limited to a nucleic acid molecule such as DNA or RNA, or a proteinaceoous molecule such as a peptide or protein" (page 4,

lines 14-16). The claims also recite "co-stimulatory molecules", however, the specification fails to define the term other than giving a few exemplary molecules such as those in page 4, lines 20-21. Claim 10 recite a fusion protein ligand comprises a costimulatory ligand portion and a viral protein portion. The specification teaches that the fusion protein comprises viral protein sequences, which function in particle assembly such that the fusion protein becomes part of a viral particle, and given a list of viruses and proteins (see page 24 and 25).

Given the broadest reasonable interpretation, the claims embrace large numbers of known or unknown compounds, costimulatory molecules, viral proteins, and fusion proteins varying in the chemical structure, physical properties, and biological functions. The specification fails to provide an adequate description to teach the structures of these molecules, other than nucleic acids and proteins; the identifying characteristics and the structure-function relationship of these broad classes of molecules and accordingly does not provide a reasonable guide for those seeking to practice the invention. Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or using it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of *any* and *all* compounds and co-stimulatory molecules.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-6 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d

731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are directed to introducing a compound into a cell comprising contacting the cells with a non-cellular particle comprises a compound and a costimulatory ligand. The specification teaches enhancing viral vaccination with costimulators such as IL-2, IL-4, and IFN-γ. However, the specification fails to teach whether any and all costimulatory molecules encompassed by the claims would enhance nucleic acid delivery. Claim 10 recite a fusion protein ligand comprises a costimulatory ligand portion and a viral protein portion. The specification teaches that the fusion protein comprises viral protein sequences, which function in particle assembly such that the fusion protein becomes part of a viral particle, and given a list of viruses and proteins (see page 24 and 25). As a preferred embodiment, the ligand is the fusion between extracellular portion of CD28 linked to a portion of HIV gp41, particularly the transmembrane and cytoplasmic portion of gp41 (page 29 and claim 12). However, the specification fails to teach that such fusion protein ligand or any fusion ligand between any viral assembly protein and any "co-stimulatory molecule" would promote the targeted nucleic acid delivery.

In view of the state of the art, targeted gene deliver is still under development and highly unpredictable. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example,

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). *Deonarain* reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Although there are efforts using fusion between viral proteins and costimulatory molecules for cell targeting, successful strategies differ in the types of viral proteins and co-stimulatory molecules used, and the region of the protein used. For example, *Capon et al* (US 6,103,521) teach targeting cells for therapeutic use by a multispecific receptor DNA sequence, which preferably use the extracellular portion of the gp41 (column 12, line 55) and intracellular portion of the CD28 (column 3, line 48); *Hurwitz et al* (US 5,741,492) teach unexpectedly enhanced immune response (meaning enhanced vaccine entry and functioning in the target cells) to mixed HIV envelop protein vaccine constructs (column 4, lines 30-67, and column 5), wherein the construct is preferably missing part or all of the transmembrane domain and /or the cytoplasmic tail domain of gp41 (portion of the gp160 transmembrane and cytoplamic regions, column 19, lines 29-33). Furthermore, as it is broadly claimed, the substantially uncountable numbers of costimulatory molecules have distinct chemical structures and biological functions. Thus, it would be highly unpredictable with respects of the function of the resulting fusion ligand selected from which costimulatory molecule and a portion thereof, and from which viral protein and a portion thereof.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for selection of these molecules so that to achieve cell targeting *in vivo* so that achieving targeted gene expression at therapeutic levels, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* and *ex vivo* gene therapy of any and all diseases or disorders, and the breadth of the claims directed to the use of numerous therapeutic genes/costimulatory (fusion) ligand combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, and 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because claims are directed to both in vitro and in vivo methods of introducing a compound into a cell, however, claims do not recite proper routes of delivery in an *in vivo* setting, it is unclear how the non-cellular particle reach the targeting cell *in vivo*.

Claim 4 is vague and indefinite because of the claim recitation "a (single) nucleotide sequences (plural)"

Claim recitation "a macrophage cell" (claim 8) is redundant since the term "macrophage" contains the meaning of a cell (a phagocytic tissue cell).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 8, 9, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by *Horspool et al* (J Immunol 1998 Mar;160:2706-2714).

The claims are directed to a method of introducing a compound into a cell comprising contacting the cell with a non-cellular particle comprising the compound and a costimulatory ligand, wherein the cell expresses costimulatory molecules, wherein the compound is a nucleic acid molecule, a DNA, wherein the DNA comprises a nucleotide sequence that encodes a protein (preferably an immunogenic protein) operably linked to regulatory elements functional in the cell, wherein the cell is a dendritic cell or a macrophage, wherein the ligand is an antibody or a native ligand of a costimulatory molecule, wherein the particle is administered to tissue of an individual.

Horspool et al teach a vaccination method of introducing a plasmid (DNA) expressing CIA (antigen) and comstimulatory molecule CD80 into the cells of Balb/c mice (see particular page 2707 and figure 5) and induced CTL response (via antigen presenting cells, such as dendritic cells and macrophages). Thus, *Horspool et al* anticipate the instant claims.

Claims 1-5, 8, 9, 11, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by *Gherardi et al* (J Immunol 1999 Jun;162:6724-33).

Gherardi et al teach a method of introducing a recombinant vaccinia virus co-expressing HIV-1 Env antigenic protein and IL-12 (costimulatory ligand), which significantly enhanced cell mediated immune response to HIV (via antigen presenting cells, such as dendritic cells and macrophages). Thus, *Gherardi et al* anticipate the instant claims.

Claims 1-4, 6, 9, 11, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by *Gallo et al* (US 6,319,504).

Gallo et al teach a method of introducing a recombinant virus vector encoding hCG protein having antiviral effect (column 4, lines 58-66, column 19, lines 38-67 to column 20). They go on to teach that the DNA construct could be linked to a ligand targeting a specific receptor (column 20, lines 6-24). Thus, *Gallo et al* anticipate the instant claims.

Claims 1-6, 8, 9, 11, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by *Dubensky Jr. et al* (US 6,342,372).

Dubensky Jr. et al teach a method using recombinant alphavirus vectors expressing heterogenous nucleic acid sequence in a eukaryotic cell (abstract, and column 3, lines 57-60). They teach that the heterogenous sequences are therapeutic proteins such as cytokines, antigenic proteins such as HIV gp120, and antisense sequences (column 4, lines 32-63). They go on to teach that the vectors could be delivered as DNA-ligand complex along with polycation compound (paragraph bridging columns 8 & 9), and include immunomodulatory cofactors (column 20, lines 43-57), such as ICAM, LFA, B7, CD28 and CTLA-4 (column 21). They teach targeting cells of macrophage (in Gaucher disease) or inducing T cell response via antigen presenting cells (dendritic cells and macrophages, column 21, lines 63-65). Thus, *Dubensky Jr. et al* anticipate the instant claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Clark can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
February 21, 2002

JAMES KETTER
PRIMARY EXAMINER